(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 March 2009 (12.03.2009)

PCT

(10) International Publication Number
WO 2009/030752 A1

(51) International Patent Classification:
C07C 317/30 (2006.01) *A61K 8/40* (2006.01)
C07C 323/30 (2006.01) *A61Q 19/00* (2006.01)
C07C 275/28 (2006.01) *A61P 17/08* (2006.01)
A61K 31/17 (2006.01) *A61P 17/10* (2006.01)
A61K 8/46 (2006.01)

(21) International Application Number:
PCT/EP2008/061779

(22) International Filing Date:
5 September 2008 (05.09.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0757395 6 September 2007 (06.09.2007) FR
60/960,095 14 September 2007 (14.09.2007) US

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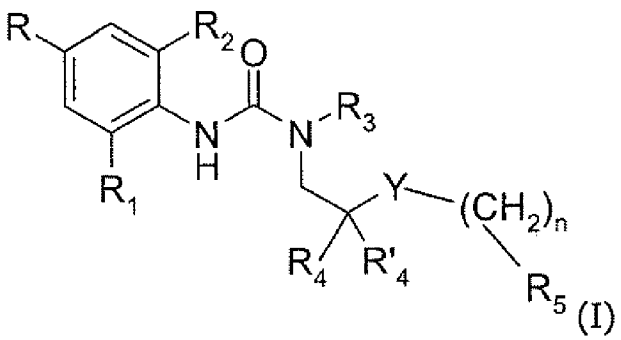
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(54) **Title:** NOVEL DERIVATIVES OF PHENYLUREAS, INHIBITORS OF THE SOAT-1 ENZYME, PHARMACEUTICAL AND COSMETIC COMPOSITIONS CONTAINING THEM



(57) **Abstract:** The present invention relates to compounds of formula (I) : as well as to cosmetic and pharmaceutical compositions containing such a compound.

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Novel derivatives of phenylureas, inhibitors of the SOAT-1 enzyme, pharmaceutical and cosmetic compositions containing them

The invention relates to novel derivatives of phenylureas, inhibitors of the SOAT-1 enzyme (abbreviation of "Sterol-O-Acyl Transferase-1", also called ACAT-1 from "Acylcoenzyme A Cholesterol Acyl Transferase"). It also relates to their use in pharmaceutical compositions intended for application in human or veterinary medicine, or in cosmetic compositions, as well as their non-therapeutic applications.

Compounds having a SOAT-1 inhibiting type of activity are widely described in the literature, as having activities in the regulation of the biological processes involving cholesterol and its derivatives. These properties endow compounds of this class with considerable potential in the treatment or prevention of a great many pathologies, and more particularly in dermatology and in cardiovascular diseases or disorders of the central nervous system. Most of the biological effects of the inhibitors of SOAT-1 are mediated by prevention of the synthesis of cholesterol esters by the SOAT-1 enzyme. Among the documents of the prior art describing SOAT-1 inhibiting molecules, we may mention for example WO96/10559, EP0370740, EP0424194, US4623663, EP0557171, US5003106, EP0293880, EP0433662, US5106873 which describe compounds for treating arteriosclerosis or hypercholesterolaemia. The therapeutic potential of the inhibitors of SOAT-1 in the treatment of cardiovascular diseases and in particular of hypercholesterolaemia and arteriosclerosis is also described in Kharbanda R. K. et al., in *Circulation*. **2005**, *11*, 804. The potential of the inhibitors of SOAT-1 for the treatment of Alzheimer's disease has also been reported in the literature, for example by Puglielli, L. et al., in *Nature Neurosciences* **2003**, *6* (4), 345.

For their part, patents US613326, US6271268, and WO2005034931 describe SOAT-1 inhibiting compounds that are able to inhibit the production of sebum. In the

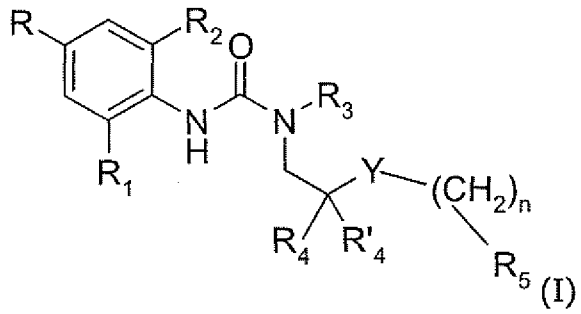
are able to inhibit the production of sebum. In the field of dermatology in particular, it is particularly advantageous to prevent excessive production of sebum and all the associated conditions.

Sebum is produced by the sebaceous glands. The highest concentration of sebaceous glands occurs on the face, the shoulders, the back and the scalp. Sebum is secreted on the surface of the skin, where it plays a very important physiological role, connected with maintenance of the dermal barrier and of a microenvironment permitting regulation of the bacterial and fungal flora of the skin.

Hyperproduction of sebum is generally associated with a skin or scalp of greasy appearance, causing discomfort and a poor appearance. Moreover, hyperproduction of sebum can give rise to seborrhoeic dermatitis and is associated with an increased incidence or severity of acne. The cholesterol esters produced in the sebaceous gland by SOAT-1 are one of the components of sebum, among several classes of lipids including triglycerides, esters of waxes and squalenes, as described by Nikkari, T., in *J Invest Derm* **1974**, *62*, 257. Inhibition of this enzyme or of other acyltransferases may therefore make it possible to inhibit the production of sebum. Patent US6133326 describes, notably, the inhibition of sebum by inhibitors of ACAT-1 (also called SOAT-1). However, to date, no treatment employing said inhibitors is commercially available. The only treatments providing cure or relief of disorders associated with hyperseborrhoea are systemic hormonal treatments or systemic treatment with 13-cis retinoic acid, and the side effects of these treatments limit their field of application considerably. There is therefore a clear medical and cosmetic need for treatment of the disorders and pathologies connected with hyperproduction of sebum.

In this context, the present invention proposes to provide novel derivatives of phenylureas, which display inhibitory action on the SOAT-1 enzyme.

The invention relates to novel derivatives of phenylureas, inhibitors of the SOAT-1 enzyme, which correspond to the following general formula (I):



(I)

in which,

- Y represents O or $S(O)_p$,

- p is equal to 0 or 2,

- n is equal to 0, 1 or 2,

- R represents a hydrogen atom, a (C_1-C_6)alkyl group, a $-CH_2-NR_6R_7$ group, a $-C(O)-NR_6R_7$ group or a $-C(S)-NR_6R_7$ group, where R_6 represents a hydrogen atom or a (C_1-C_4)alkyl group and R_7 represents a hydrogen atom, a phenyl or a cycloalkyl group,

- R_1 represents a hydrogen atom, a (C_1-C_6)alkyl group or an atom of chlorine, bromine or fluorine,

- R_2 represents a (C_1-C_6)alkyl group,

- R_3 represents a hydrogen atom or a (C_1-C_6)alkyl group,

- R_4 and R'_4 are identical and represent a (C_1-C_6)alkyl group or alternatively R_4 and R'_4 are joined together

and form, with the carbon atom to which they are attached, a cycloalkyl group, an indanyl group, or a saturated heterocyclic group selected from the groups piperidine, tetrahydropyran, pyrrolidine, tetrahydrothiophene, tetrahydrofuran and azetidine, moreover the groups piperidine, pyrrolidine and azetidine can optionally be substituted, on the nitrogen atom, with an R_8, $-C(O)R_8$ or $-SO_2R_8$ group, where R_8 represents a (C_1-C_4)alkyl group,

- R_5 represents an unsubstituted phenyl group or a phenyl group substituted with one to three substituents, which may be identical or different, selected from the atoms of chlorine, bromine or fluorine, the groups (C_1-C_6)alkyl, cycloalkyl, trifluoromethyl, hydroxy, phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, (C_1-C_6)alkoxy, phenoxy, (C_1-C_6)alkylthio, trifluoromethoxy, or $-NR_9R_{10}$, where R_9 and R_{10}, which may be identical or different, represent, each independently, a hydrogen atom or a (C_1-C_4)alkyl group,

as well as their pharmaceutically acceptable salts, solvates or hydrates.

"Alkyl group" means a saturated, linear or branched hydrocarbon chain. (C_1-C_6)alkyl means an alkyl chain having from 1 to 6 carbon atoms. As an example of (C_1-C_6)alkyl, we may mention the methyl, ethyl, n-propyl, isopropyl, n-butyl, *tert*-butyl, sec-butyl, pentyl, and hexyl groups. (C_1-C_4)alkyl means an alkyl chain having from 1 to 4 carbon atoms. As an example of (C_1-C_4)alkyl, we may mention the methyl, ethyl, n-propyl, isopropyl, n-butyl, *tert*-butyl, and sec-butyl groups.

(C_1-C_6)alkoxy denotes an $-O-(C_1-C_6)$alkyl group.

(C_1-C_6)alkylthio denotes an $-S-(C_1-C_6)$alkyl group.

Phenoxy denotes an -O-phenyl group.

"Cycloalkyl group" denotes a saturated, cyclic hydrocarbon chain, having from 3 to 7 carbon atoms. As an example of cycloalkyl group, we may mention the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl groups.

The compounds of formula (I) defined above are preferred, in which:

- Y represents O, $S(O)_p$,

- p is equal to 0 or 2,

- n is equal to 0, 1 or 2,

- R represents a hydrogen atom,

- R_1 represents a methyl, ethyl, isopropyl or *tert*-butyl group,

- R_2 represents a methyl, ethyl, isopropyl or *tert*-butyl group,

- R_3 represents a hydrogen atom,

- R_4 and R'_4 are identical and represent an ethyl group or alternatively R_4 and R'_4 are joined together and form, with the carbon atom to which they are attached, either a cyclopentyl, cyclohexyl, cycloheptyl, or indanyl group, or a tetrahydropyran group, piperidine group, or piperidine group substituted on the nitrogen atom with an R_8, $-C(O)R_8$ or $-SO_2R_8$ group, where R_8 represents a (C_1-C_4)alkyl group,

- R_5 represents an o-, m-, or p-biphenyl, o-, m- or p-iodophenyl, o-, m-, or p-(2-pyridyl)phenyl, o-, m-, or p-(3-pyridyl)phenyl or o-, m-, or p-(4-pyridyl)phenyl group, an unsubstituted phenyl group, a phenyl group substituted with one to three substituents, identical

or different, selected from methyl, ethyl, trifluoromethyl, fluorine, chlorine, hydroxy,

as well as their pharmaceutically acceptable salts, solvates or hydrates.

According to the present invention, among the compounds of formula (I) as defined above, those are more particularly preferred that have one or a combination of the following characteristics, when they are not mutually exclusive:

- n is equal to 0 or 1,

- R represents a hydrogen atom,

- R_1 represents an isopropyl group,

- R_2 represents an isopropyl group,

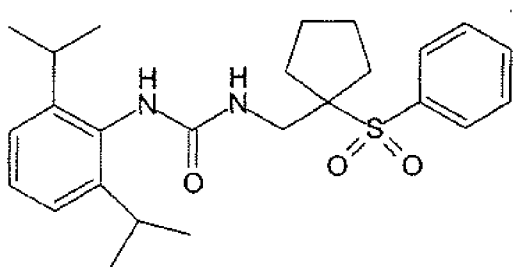
- R_3 represents a hydrogen atom,

- R_4 and R'_4 are joined together and form, with the carbon atom to which they are attached, a cyclopentyl, cyclohexyl or indanyl group,

- R_5 represents an unsubstituted phenyl group or a phenyl group substituted with a methyl group, for example in the para position, or with a phenyl group, for example in the ortho position.

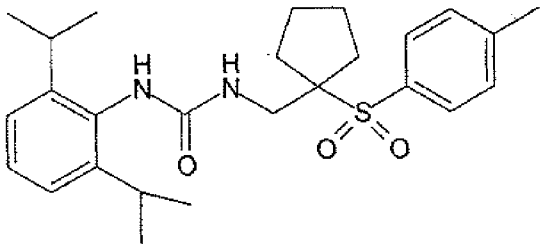
The compounds of formula (I) given below, as well as their pharmaceutically acceptable salts, solvates or hydrates, are particularly preferred:

-1-(1-Benzenesulphonyl-cyclopentylmethyl)-3-(2,6-diisopropyl-phenyl)-urea, compound (I.1) with Y = $-S(O)_p$, p=2, n= 0, R = H, $R_1 = R_2$= iPr; R_3 = H; R_4 and R'_4 are joined together to form a cyclopentyl; R_5 = Ph



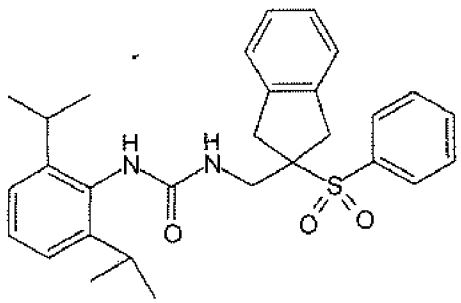
(I.1)

-1-(2,6-Diisopropyl-phenyl)-3-[1-(toluene-4-sulphonyl)-cyclopentylmethyl]-urea, compound (I.2) with Y = $-S(O)_p$, p=2, n= 0, R = H, R_1 = R_2= iPr; R_3 = H; R_4 and R'_4 are joined together to form a cyclopentyl; R_5 = p-tolyl



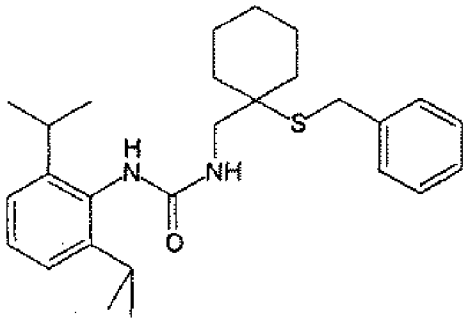
(I.2)

-1-(2-Benzenesulphonyl-indan-2-ylmethyl)-3-(2,6-diisopropyl-phenyl)-urea, compound (I.3) with Y = $-S(O)_p$, p=2, n= 0, R = H, R_1 = R_2= iPr; R_3 = H; R_4 and R'_4 are joined together to form an indanyl; R_5 = Ph



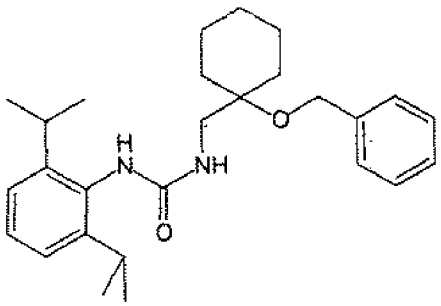
(I.3)

-1-(1-Benzylsulphanyl-cyclohexylmethyl)-3-(2,6-diisopropyl-phenyl)-urea, compound (I.4) with Y = S, p = 0, n= 1, R = H, R_1 = R_2= iPr; R_3 = H; R_4 and R'_4 are joined together to form a cyclohexyl; R_5 = Ph



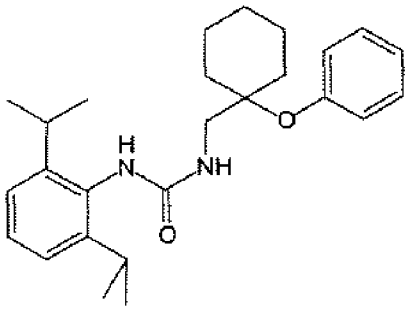
(I.4)

-1-(1-Benzyloxy-cyclohexylmethyl)-3-(2,6-diisopropyl-phenyl)-urea, compound (I.5) with Y = O, p = 0, n= 1, R = H, R_1 = R_2= iPr; R_3 = H; R_4 and R'_4 are joined together to form a cyclohexyl; R_5 = Ph



(I.5)

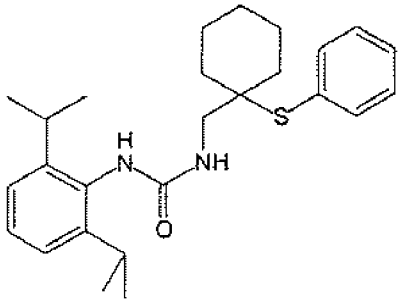
-1-(2,6-Diisopropyl-phenyl)-3-(1-phenoxy-cyclohexylmethyl)-urea, compound (I.6) with Y = O, p = 0, n= 0, R = H, R_1 = R_2= iPr; R_3 = H; R_4 and R'_4 are joined together to form a cyclohexyl; R_5 = Ph



(I.6)

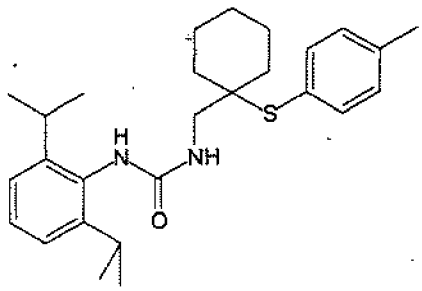
-1-(2,6-Diisopropyl-phenyl)-3-(1-phenylsulphanyl-cyclohexylmethyl)-urea, compound (I.7) with Y = S, p =

0, n= 0, R = H, R_1 = R_2= iPr; R_3 = H; R_4 and R'_4 are joined together to form a cyclohexyl; R_5 = Ph



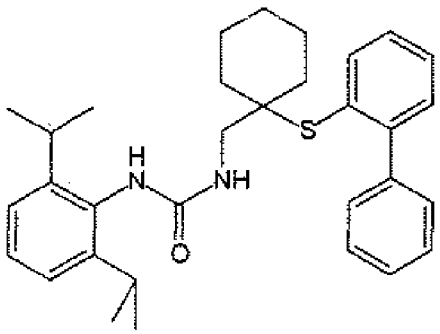
(I.7)

-1-(2,6-Diisopropyl-phenyl)-3-(1-p-tolylsulphanyl-cyclohexylmethyl)-urea, compound (I.8) with Y = S, p = 0, n= 0, R = H, R_1 = R_2= iPr; R_3 = H; R_4 and R'_4 are joined together to form a cyclohexyl; R_5 = p-tolyl



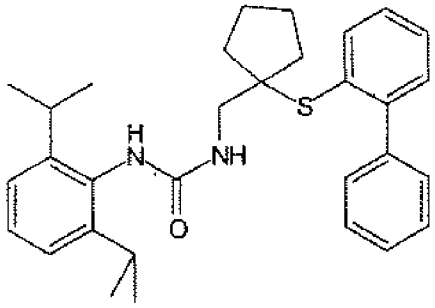
(I.8)

-1-[1-(Biphenyl-2-ylsulphanyl)-cyclohexylmethyl]-3-(2,6-diisopropyl-phenyl)-urea, compound (I.9) with Y = S, p = 0, n = 0, R = H, R_1 = R_2= iPr; R_3 = H; R_4 and R'_4 are joined together to form a cyclohexyl; R_5 = o-BiPh



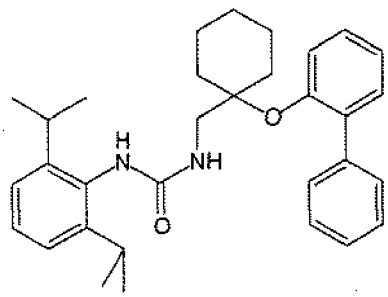
(I.9)

-1-[1-(Biphenyl-2-ylsulphanyl)-cyclopentylmethyl]-3-(2,6-diisopropyl-phenyl)-urea, compound (I.10) with Y = S, p = 0, n = 0, R = H, R_1 = R_2= iPr; R_3 = H; R_4 and R'_4 are joined together to form a cyclopentyl; R_5 = o-BiPh



(I.10)

-1-[1-(Biphenyl-2-yloxy)-cyclohexylmethyl]-3-(2,6-diisopropyl-phenyl)-urea, compound (I.11) with Y = O, n = 0, R = H, R_1 = R_2= iPr; R_3 = H; R_4 and R'_4 are joined together to form a cyclohexyl; R_5 = o-BiPh



(I.11)

The salts of the compounds according to the invention are prepared according to methods that are well known by a person skilled in the art. The salts of the compounds of formula (I) according to the present invention include those with organic or mineral acids that permit convenient separation or crystallization of the compounds of formula (I), as well as pharmaceutically acceptable salts. We may mention, as a suitable acid: picric acid, oxalic acid or an optically active acid, for example a tartaric acid, a dibenzoyltartaric acid, a mandelic acid or a camphosulphonic acid, and those which form

physiologically acceptable salts, such as the hydrochloride, hydrobromide, sulphate, hydrogen-sulphate, dihydrogen-phosphate, maleate, fumarate, 2-naphthalenesulphonate, paratoluenesulphonate, the hydrochloride being preferred.

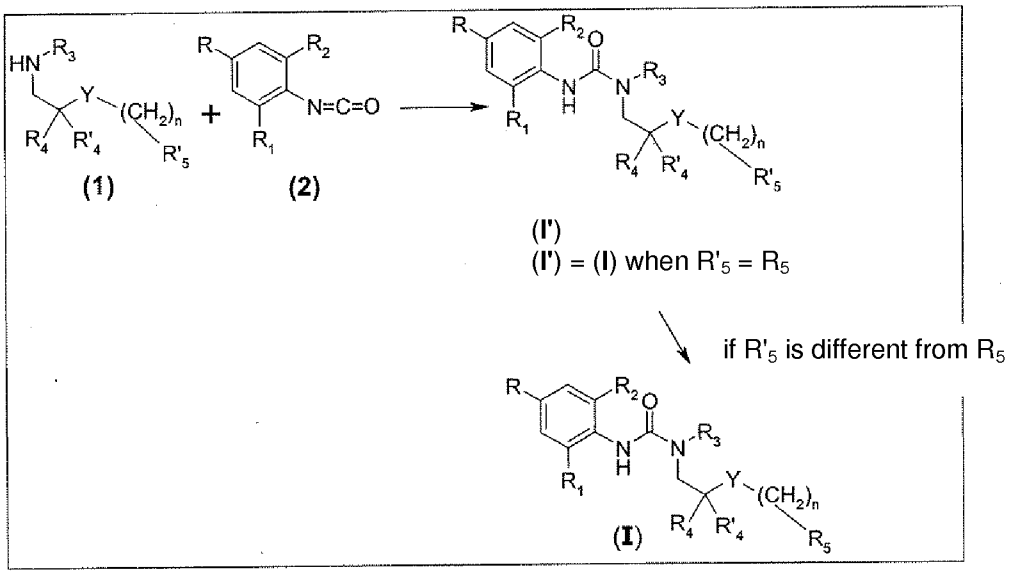
The solvates or hydrates can be obtained directly at the end of the synthesis process, compound (I) being isolated in the form of a hydrate, for example a mono or hemi-hydrate or of a solvate of the solvent of reaction or purification.

The compounds of formula (I) can be purified by any conventional method of purification, for example by crystallization or purification by column chromatography.

When a compound of formula (I) according to the invention has one or more asymmetric carbons, the optical isomers of this compound form an integral part of the invention. The compound of formula (I) can therefore be in the form of a pure isomer or a mixture of isomers in all proportions.

The compounds of formula (I) according to the invention can be prepared according to **SCHEME 1** given below, in which R, R_1, R_2, R_3, R_4, R'_4, Y and n are as defined for the compounds of formula (I) and R'_5 represents the group R_5 or a group that is a precursor of R_5:

SCHEME 1

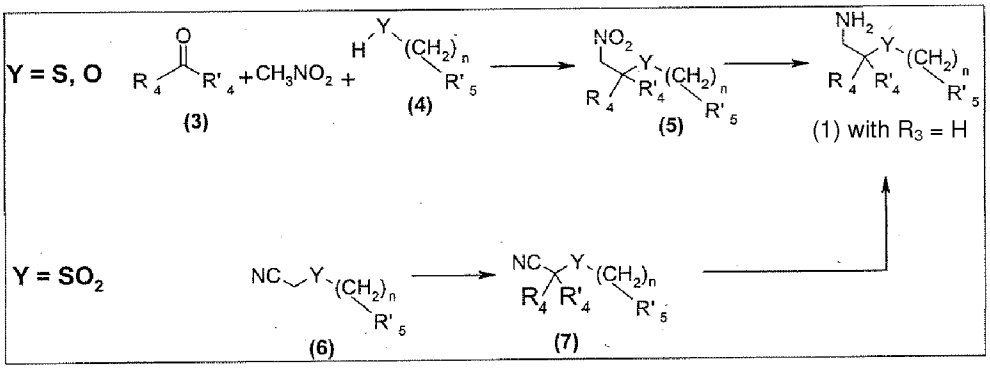


The compounds of general formula (I) can be prepared by addition of the primary or secondary amines of general formula (**1**) to the corresponding urea precursors, for example the isocyanates (**2**), for example in accordance with the reactions described by O'Brien, P. M. et al. in *J Med Chem* **1994**, *37* (12), 1810-1822. The compound of formula (**1**) can bear the R_5=R'_5 group of the desired final compound of formula (I) directly and in this case the compound (I') corresponds to the desired compound (I), which is the case for example when R_5 = o, m, or p-iodo-phenyl. In some cases, the addition can be performed with a compound of formula (**1**) bearing a group R'_5 that is a precursor of group R_5, to form an intermediate (I') which must then be converted to obtain the desired group R_5. For example, in the preparation of compounds of formula (I) in which R_5 = o, m, or p-biphenyl or indeed any isomers of phenyl-pyridine, the compound of formula (**1**) used comprises a group R'_5 = o, m, or p-iodo-phenyl, the iodine being in the position corresponding to the desired phenyl or pyridyl group. The compound of formula (I') which corresponds to the compound of formula (I) in which R'_5 = o, m, or p-iodo-phenyl is formed as an intermediate is then submitted to a Suzuki type of coupling reaction

or similar, with a corresponding phenylboronic acid or pyridylboronic acid partner, according to the conventional conditions described for example in Suzuki et al., *Synth. Commun.* **1981**, *11*, 513 or Sharp, M.J. *Tet. Lett.* **1985**, *26*, 5997) or optimized conditions if necessary (see for example Littke, A.F. et al., *J Am Chem Soc* **2000**, *122* (17), 4020-4028).

The primary amines of general formula (**1**) in which R_3 = H can be prepared according to **SCHEME 2** given below, in which R_4, R'_4, Y and n are as defined for the compounds of formula (I) and R'_5 represents the group R_5 or a group that is a precursor of R_5:

SCHEME 2



In the case when Y = O or S, the ketones of formula (**3**) are reacted with nitromethane in a basic medium and then the nucleophile thiol (Y=S) or alcohol (Y=O) of formula (**4**) is added by a reaction of the Mickaël type to give the nitrated compounds of formula (**5**), as described for example in Lin, W.-W. et al. *J Org Chem* **2001**, *66* (6), 1984-1991 and Schneider, R. et al. *J Heterocycl Chem* **1994**, *31* (4), 797-803. The nitro function of the compounds of formula (**5**) can then be reduced to give the primary amine (1), for example by reaction with $LiAlH_4$, as described in Hegedus, L S.; Perry, R. J.; *J Org Chem* **1984**, *49* (14), 2570.

In the case when Y = SO_2, the nitriles of formula (**7**) can be obtained by deprotonation of the acidic methylene of the compounds of formula (**6**), then substitution with an electrophile R_4-X (=R'_4-X) where X is a leaving group such as a chlorine (with two equivalents, or one equivalent in the case when R_4 and R'_4 are joined together to form a ring), for example in accordance with the conditions described in Sakamoto, T. et al., *Heterocycles* **1988**, *27*, 1353. Once again, reduction of the nitrile function of the compound of formula (**7**), for example by reaction with a hydride as described above, permits the primary amines of formula (**1**) to be obtained.

The isocyanates of formula (**2**) are commercial compounds or can be prepared by techniques that are well known to a person skilled in the art.

The functional groups that are optionally present in the reaction intermediates used in the method can be protected, either permanently or temporarily, by protecting groups that ensure definite synthesis of the expected compounds. The reactions of protection and deprotection are performed according to techniques that are well known by a person skilled in the art. Temporary protecting group of amines, alcohols or of carboxylic acids means protecting groups such as those described in "Protective Groups in Organic Chemistry", ed. McOmie J.W.F., Plenum Press, 1973, in "Protective Groups in Organic Synthesis", 2nd edition, Greene T.W. and Wuts P.G.M., publ. John Wiley and Sons, 1991 and in "Protecting Groups», Kocienski P.J., 1994, Georg Thieme Verlag.

The compounds (I) according to the invention, as well as their pharmaceutically acceptable salts, solvates and/or hydrates, display SOAT-1 enzyme inhibiting properties. This inhibitory effect on the SOAT-1 enzyme is measured by a primary HepG2 enzyme test, as

described below. The preferred compounds according to the present invention have a concentration permitting 50% inhibition of the enzyme response (IC_{50}) less than or equal to 1200 nM, preferably less than or equal to 500 nM, and advantageously less than or equal to 100 nM.

The present invention also relates to the compounds of formula (I) as described above, as well as their pharmaceutically acceptable salts, pharmaceutically acceptable solvates and/or hydrates, as a medicinal product.

The present invention relates to the use of at least one compound of formula (I), as well as its salts, pharmaceutically acceptable solvates and/or hydrates, for the manufacture of a medicinal product for preventing and/or treating disorders of the sebaceous gland such as hyperseborrhoea, acne, seborrhoeic dermatitis, atopic dermatitis or rosacea, ocular pathologies such as ocular rosacea, disorders of the meibomian gland, such as blepharitis, meibomitis, chalazion, dry eye, conjunctivitis or keratoconjunctivitis or else pathologies such as hypercholesterolaemia, arteriosclerosis or Alzheimer's disease. The compounds according to the invention are particularly suitable for the manufacture of a pharmaceutical composition intended for the treatment of acne. The compounds according to the invention are thus also suitable for use in the pathologies listed above.

The present invention also relates to a pharmaceutical or cosmetic composition comprising, in a physiologically acceptable medium, at least one compound of formula (I) as defined above, or one of its salts, pharmaceutically acceptable solvates and/or hydrates. The compositions according to the invention therefore comprise a physiologically acceptable carrier

or at least one physiologically or pharmaceutically acceptable excipient, selected according to the desired cosmetic or pharmaceutical form and the chosen method of administration.

Physiologically acceptable carrier or medium means a carrier that is compatible with the skin, the mucosae and/or the integumentary appendages.

The composition according to the invention can be administered by the enteral, parenteral, rectal, topical or ocular route. Preferably, the pharmaceutical composition is packaged in a form suitable for topical application.

For administration by the enteral route, the composition, more particularly the pharmaceutical composition, can be in the form of tablets, capsules, coated tablets, syrups, suspensions, solutions, powders, granules, emulsions, microspheres or nanospheres or lipid or polymeric vesicles permitting controlled release. For parenteral administration, the composition can be in the form of solutions or suspensions for infusion or for injection.

The compositions according to the invention contain a compound according to the invention, in sufficient quantity to obtain the desired cosmetic, prophylactic or therapeutic effect. The compounds according to the invention are generally administered at a daily dose from about 0.001 mg/kg to 100 mg/kg of body weight, in 1 to 3 doses. The compounds are used systemically at a concentration generally between 0.001 and 10 wt.%, preferably between 0.01 and 2 wt.%, relative to the weight of the composition.

For topical administration, the pharmaceutical composition according to the invention is intended more particularly for the treatment of the skin and of the

mucosae and can be in the form of unguents, creams, milks, ointments, powders, impregnated tampons, syndets, solutions, gels, sprays, mousses, suspensions, stick lotions, shampoos, or washing bases. It can also be in the form of suspensions of microspheres or nanospheres or lipid or polymeric vesicles or polymeric patches and hydrogels permitting controlled release. This composition for topical administration can be in anhydrous form, in aqueous form or in the form of an emulsion.

The compounds are used topically at a concentration generally between 0.001 and 10 wt.%, preferably between 0.01 and 2 wt.%, relative to the total weight of the composition.

The compounds of formula (I) according to the invention, as well as their salts, pharmaceutically acceptable solvates and/or hydrates, also find application in the cosmetics field, in particular in body and hair hygiene and more particularly for combating or preventing greasy skin, greasy hair or greasy scalp.

The invention therefore also relates to the cosmetic use of a composition comprising, in a physiologically acceptable carrier, at least one of the compounds of formula (I), optionally in the form of a salt, pharmaceutically acceptable solvate and/or hydrate, for body or hair hygiene.

The cosmetic composition according to the invention containing, in a cosmetically acceptable carrier, at least one compound of formula (I) or one of its salts, pharmaceutically acceptable solvates and/or hydrates, can notably be in the form of a cream, a milk, a lotion, a gel, an unguent, an ointment, suspensions of microspheres or nanospheres or lipid or polymeric

vesicles, impregnated tampons, solutions, sprays, mousses, sticks, soaps, shampoos or washing bases.

The concentration of compound of formula (I) in the cosmetic composition is between 0.001 and 3 wt.%, relative to the total weight of the composition.

The pharmaceutical and cosmetic compositions described above can in addition contain additives that are inert, or even pharmacodynamically active in the case of pharmaceutical compositions, or combinations of these additives, and notably:

- wetting agents;
- flavour-improving agents;
- preservatives such as esters of parahydroxybenzoic acid;
- stabilizers;
- moisture regulators;
- pH regulators;
- agents for modifying osmotic pressure;
- emulsifiers;
- UV-A and UV-B filters;
- antioxidants, such as α-tocopherol, butylated hydroxyanisole or butylated hydroxytoluene, superoxide dismutase, ubiquinol or certain chelators of metals;
- depigmenting agents such as hydroquinone, azelaic acid, caffeic acid or kojic acid;
- emollients;
- moisturizers such as glycerol, PEG 400, thiamorpholinone, and derivatives thereof or urea;
- carotenoids and, notably, β-carotene;
- α-hydroxy acids and α-keto acids or their derivatives, such as lactic, malic, citric, glycolic, mandelic, tartaric, glyceric, and ascorbic acids, as well as their salts, amides or esters, or β-hydroxy acids or their derivatives, such as salicylic acid as well as their salts, amides or esters.

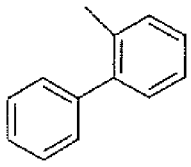
Of course, a person skilled in the art will take care to select a compound or compounds to be added to these compositions in such a way that the advantageous properties associated intrinsically with the present invention are not, or substantially are not, altered by the addition envisaged.

Moreover, in a general way, the same preferences as those previously mentioned for the compounds of formula (I) apply *mutatis mutandis* to the medicinal products, cosmetic and pharmaceutical compositions and applications employing the compounds of the invention.

By way of illustration and in no way limiting, several examples of preparation of active compounds of formula (I) according to the invention are presented below, as well as the results for the biological activity of said compounds.

The following abbreviations are used:

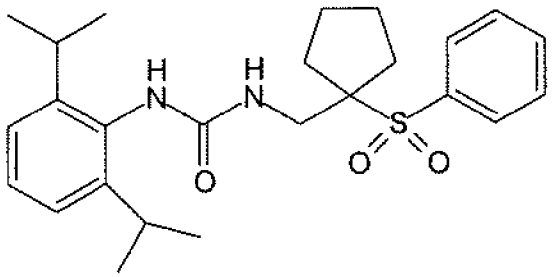
iPr = isopropyl, Ph = phenyl, p-tolyl = 4-methylphenyl, p = para, m = meta, o = ortho, BiPh = biphenyl, Me = methyl,

o-biphenyl = o-BiPh = 

Example 1

1-(1-Benzenesulphonyl-cyclopentylmethyl)-3-(2,6-diisopropyl-phenyl)-urea, compound (I.1)

where Y = $-S(O)_p$, p=2, n= 0, R = H, R_1 = R_2= iPr; R_3 = H; R_4 and R'_4 are joined together to form a cyclopentyl; R_5 = pH



(I.1)

a/ 1-Benzenesulphonyl-cyclopentanecarbonitrile

629 mg (2.8 mmol) of benzyltriethylammonium chloride is added to 5 g (27.6 mmol) of benzenesulphonylacetonitrile and 6.55 g (30.3 mmol) of 1,4-dibromobutane in 50 ml of a 50% aqueous soda solution. The reaction mixture is stirred at room temperature for 3 h. It is then diluted with water and extracted with ethyl acetate. The organic phases are combined and washed with water. They are dried over magnesium sulphate, filtered and the solvents are evaporated. The residue is purified on silica gel (heptane/ethyl acetate, 50/50, v/v). 6.35 g of 1-benzenesulphonyl-cyclopentanecarbonitrile is obtained in the form of a beige powder. (Yield = 98%).

b/ C-(1-Benzenesulphonyl-cyclopentyl)-methylamine

194 mg (5.1 mmol) of lithium aluminium hydride is added to a solution of 1 g (4.2 mmol) of 1-benzenesulphonyl-cyclopentanecarbonitrile in 20 ml of tetrahydrofuran. The reaction mixture is stirred at room temperature (RT) for 20 h. It is then hydrolysed with 194 µl of water, 194 µl of a 15% soda solution and then 582 µl of water, stirred for 5 minutes, then filtered. The filtrate is evaporated and the residue is chromatographed on silica gel (dichloromethane then dichloromethane/methanol, 90/10, v/v). 420 mg of C-(1-benzenesulphonyl-cyclopentyl)-methylamine is obtained in the form of a colourless oil. (Yield= 42%).

c/ 1-(1-Benzenesulphonylcyclopentylmethyl)-3-(2,6-diisopropyl-phenyl)-urea

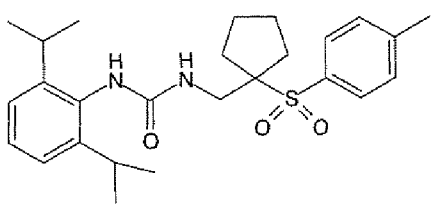
In a tube, under nitrogen, 157 mg (0.77 mmol) of 2-isocyanato-1,3-diisopropylbenzene is added to a solution of 168 mg (0.7 mmol) of C-(1-benzenesulphonyl-cyclopentyl)-methylamine in 3.5 ml of dichloromethane. The reaction mixture is stirred at RT for 3h. The solvent is evaporated with a nitrogen stream. The paste obtained is taken up in heptane (5 mL) for crystallization. The white powder obtained is chromatographed on silica gel (dichloromethane then dichloromethane/methanol, 98/2, v/v). The oil obtained is crystallized from heptane. After filtration and drying, 135 mg of 1-(1-benzenesulphonylcyclopentylmethyl)-3-(2,6-diisopropyl-phenyl)-urea is obtained in the form of a white powder (m.p. = 124°C, Yield= 44%).

^{1}H NMR ($CDCl_3$, 400 MHz): 1.19-1.33 (m, 12H), 1.56(m, 2H), 1.66(m, 4H), 2.41(m, 2H), 3.29(m, 2H), 3.4(d, J=4.8Hz, 2H), 5.46(br, ~1H), 6.06(br, 1H), 7.23-7.26(m, 2H), 7.37(t, J=7.6Hz, 1H), 7.46-7.50(m, 2H), 7.6-7.66(m, 3H).

Example 2

1-(2,6-Diisopropyl-phenyl)-3-[1-(toluene-4-sulphonyl)-cyclopentylmethyl]-urea, compound (I.2)

where Y = -S(O)$_p$, p=2, n= 0, R = H, R_1 = R_2= iPr; R_3 = H; R_4 and R'$_4$ are joined together to form a cyclopentyl; R_5 = p-tolyl



(I.2)

a/ (Toluene-4-sulphonyl)-acetonitrile.

3.37 g (28 mmol) of bromoacetonitrile and 640 mg (2.8 mmol) of benzyltriethylammonium chloride are added to a solution of 5 g (28 mmol) of sodium 4-methyl-benzenesulphinate in 50 ml of toluene and 50 ml of dimethylformamide. The reaction mixture is stirred at room temperature for 24h. The heterogeneous mixture is filtered. The filtrate is evaporated and then purified on silica gel (heptane then heptane/ethyl acetate, 60/40 v/v). The product is triturated in heptane then filtered and dried. 2.95g of (toluene-4-sulphonyl)-acetonitrile is obtained in the form of a pale yellow powder. (Yield= 54%).

b/ 1-(Toluene-4-sulphonyl)-cyclopentanecarbonitrile.

Similarly to Example 1 paragraph a), by reaction of 2 g (10.2 mmol) of (toluene-4-sulphonyl)-acetonitrile with 1.35 ml (11.3 mmol) of 1,4-dibromobutane, 50 ml of aqueous soda solution, 233 mg (1 mmol) of benzyltriethylammonium chloride. 2.14 g of 1-(toluene-4-sulphonyl)cyclopentanecarbonitrile is obtained in the form of a brown powder. (Yield= 84%)

c/ C-[1-(Toluene-4-sulphonyl)-cyclopentyl]-methylamine.

Similarly to Example 1 b), by reaction of 1.1 g (4.4 mmol) of 1-(toluene-4-sulphonyl)-cyclopentanecarbonitrile with 200 mg of aluminium lithium hydride. 400 mg of C-[1-(toluene-4-sulphonyl)-cyclopentyl]-methylamine is obtained in the form of an orange solid. (Yield= 36%).

d/ 1-(2,6-Diisopropyl-phenyl)-3-[1-(toluene-4-sulphonyl)-cyclopentylmethyl]-urea.

Similarly to Example 1 c), by reaction of 200 mg (0.8 mmol) of C-[1-(toluene-4-sulphonyl)-cyclopentyl]-methylamine with 177 mg (0.87 mmol) of 2-isocyanato-

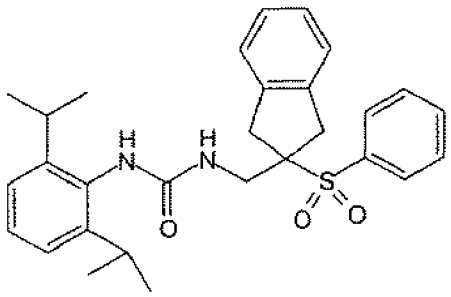
1,3-diisopropyl-benzene. 276 mg of 1-(2,6-diisopropyl-phenyl)-3-[1-(toluene-4-sulphonyl)cyclopentylmethyl]-urea is obtained in the form of an off-white powder. (Yield= 77%).

^{1}H NMR ($CDCl_3$, 400 MHz): 1.19-1.32(m, 12H), 1.53-1.67(m, 6H), 2.11-2.18(m, 2H), 2.42(s, 3H), 3.29(m, 2H), 3.40(d, J=5.2Hz, 2H), 5.51(br, 1H), 5.78(br, 1H), 7.23-7.28(m, 4H), 7.37(t, J=8.0Hz, 1H), 7.52(br, 2H).

Example 3

1-(2-Benzenesulphonyl-indan-2-ylmethyl)-3-(2,6-diisopropyl-phenyl)-urea, compound (I.3)

where Y = $-S(O)_p$, p=2, n= 0, R = H, R_1 = R_2= iPr; R_3 = H; R_4 and R'_4 are joined together to form an indanyl; R_5 = Ph



(I.3)

a/ 2-Benzenesulphonyl-indane-2-carbonitrile.

Similarly to Example 1 a), by reaction of 5 g (27.6 mmol) of benzenesulphonyl-acetonitrile with 8 g (30.4 mmol) of a,a'-dibromo-o-xylene, 50 ml of aqueous soda solution, 629 mg (2.8 mmol) of benzyltriethylammonium chloride. 2.1 g of 2-benzenesulphonyl-indane-2-carbonitrile is obtained in the form of a white solid. (Yield= 27%).

b/ C-(2-Benzenesulphonyl-indan-2-yl)-methylamine.

Similarly to Example 1 b), by reaction of 1 g (3.5 mmol) of 2-benzenesulphonyl-indane-2-carbonitrile with 161 mg (4.2 mmol) of lithium aluminium hydride. 168 mg of C-(2-benzenesulphonyl-indan-2-yl)-methylamine is obtained in the form of a brown oil. (Yield= 17%).

c/ 1-(2-Benzenesulphonyl-indan-2-ylmethyl)-3-(2,6-diisopropyl-phenyl)-urea.

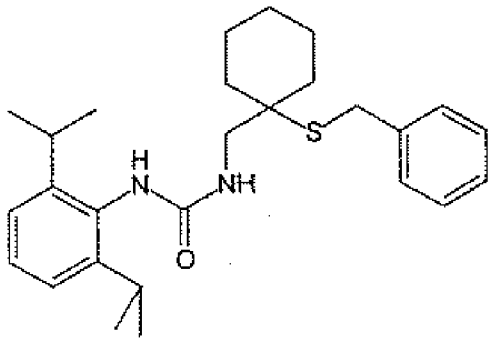
Similarly to Example 1 c), by reaction of 168 mg (0.6 mmol) of C-(2-benzenesulphonyl-indan-2-yl)-methylamine with 131 mg (0.64 mmol) of 2-isocyanato-1,3-diisopropyl-benzene. 106 mg of 1-(2-benzenesulphonyl-indan-2-ylmethyl)-3-(2,6-diisopropyl-phenyl)-urea is obtained in the form of a white solid. (Yield= 36%).

^{1}H NMR ($CDCl_3$, 400 MHz): 1.2-1.38 (m, 12H), 2.96(d, J=16.7Hz, 2H), 3.31(m, 2H), 3.55(d, J=16.8Hz, 2H), 3.64(d, J=5.2Hz, 2H), ~5.55(br, 1H), 5.80(br, 1H), 7.05 (m, 4H), 7.26 (s, 2H), 7.43(m, 3H), 7.6(m, 1H), 7.65(br, 2H).

Example 4

1-(1-Benzylsulphanyl-cyclohexylmethyl)-3-(2,6-diisopropyl-phenyl)-urea, compound (I.4)

where Y = S, p = 0, n= 1, R = H, R_1 = R_2= iPr; R_3 = H; R_4 and R'_4 are joined together to form a cyclohexyl; R_5 = Ph



(I.4)

a/ (1-Nitromethyl-cyclohexylsulphanylmethyl)-benzene.

1.05 ml (10 mmol) of cyclohexanone, 5.5 ml (101 mmol) of nitromethane, 2.1 ml (21 mmol) of piperidine are added to a solution of 5 ml (42 mmol) of benzylmercaptan in 20 ml of acetonitrile. The solution is refluxed for 4 h. At room temperature, the mixture is evaporated and the residue is chromatographed on silica gel (heptane then heptane/ethyl acetate, 50/50, v/v). 600 mg of (1-nitromethyl-cyclohexylsulphanylmethyl)-benzene is obtained in the form of a colourless oil. (Yield= 22%).

b/ C-(1-Benzylsulphanyl-cyclohexyl)-methylamine.

A solution of 500 mg (1.88 mmol) of (1-nitromethyl-cyclohexyl-sulphanylmethyl)-benzene in 20 ml of ethyl ether is added dropwise to 86 mg (2.26 mmol) of lithium aluminium hydride in 10 ml of ethyl ether at 0°C. It is stirred for 2 hours at 0°C. The reaction is stopped by adding 100µl of water, 100µl of 15% soda and then 500 µl of water. The mixture is then filtered on Celite and the filtrate is evaporated. The residue is purified on silica gel (heptane/ethyl acetate, 50/50, v/v then ethyl acetate then ethyl acetate/methanol, 50/50 v/v). 125 mg of C-(1-benzylsulphanyl-cyclohexyl)-methylamine is obtained in the form of a colourless oil. (Yield= 28%).

c/ 1-(1-Benzylsulphanyl-cyclohexylmethyl)-3-(2,6-diisopropyl-phenyl)-urea.

Similarly to Example 1 c), by reaction of 120 mg (0.51 mmol) of C-(1-benzylsulphanyl-cyclohexyl)-methylamine with 125 µl (0.61 mmol) of 2,6-diisopropylphenylisocyanate. 101 mg of 1-(1-benzylsulphanyl-cydohexylmethyl)-3-(2,6-diisopropyl-phenyl)-urea is obtained in the form of a white solid. (m.p. = 156°C, Yields 45%).

Mass: 439. HPLC: 96.6%.

^{1}H NMR ($CDCl_3$, 400 Mz): 1.18 (s, 6H); 1.23 (s, 6H); 1.41-1.65 (m, 10H); 3.24-3.24 (d, 2H); 3.26-3.36 (m, 2H); 3.43 (s, 2H); 4.75 (s, 1H); 5.70 (s, 1H); 7.01 (s, 2H); 7.17 (d, 3H); 7.25-7.28 (m, 2H); 7.38-7.42 (m, 1H).

Example 5: Biological tests

The compounds of formula (I) according to the invention were tested to evaluate their inhibitory activity with respect to the enzyme ACAT-1 based on the following work: "Identification of ACAT1- and ACAT2-specific inhibitors using a novel, cell based fluorescence assay: individual ACAT uniqueness", J.lipid.Res (2004) vol 45, pages 378-386. The principle of this test is based on the use of NBD-cholesterol, an analogue of cholesterol with fluorescence depending on its environment. When it is in a polar environment it is weakly fluorescent, whereas in a non-polar environment it is strongly fluorescent. Free NBD-cholesterol localizes in the cell membranes and is weakly fluorescent in this polar environment. When NBD-cholesterol is esterified by ACAT, the ester of NBD-cholesterol localizes in the non-polar lipid droplets and is then strongly fluorescent.

The following method is used: HepG2 cells are incubated in the presence of NBD-cholesterol (1 µg/ml) and of the test compound of formula (I) in black, transparent-bottom 96-well plates at a rate of 30000 cells per well. After incubation for 6h at 37°C, under 5% CO_2, the mixture is removed by inversion and the cells are washed with 2 × 100 µl of PBS. After adding 50 µl of lysis buffer ($NaPO_4$ 10 mM, Igepal 1%) the plates are agitated for 5 min and read in fluorescence (excitation 490 nm, emission 540 nm) on a FUSION instrument (Perkin Elmer). As an illustration, an IC_{50} of 71 nM is obtained for compound (I.4)

Example 6: Examples of formulation

Various actual formulations based on the compounds according to the invention are shown below.

A- ORAL ADMINISTRATION

(a) Tablet of 0.2 g

- Compound (**I.3**)	0.001 g
- Starch	0.114 g
- Dicalcium phosphate	0.020 g
- Silica	0.020 g
- Lactose	0.030 g
- Talc	0.010 g
- Magnesium stearate	0.005 g

(b) Oral suspension in 5 ml ampoules

- Compound (**I.1**)	0.001 g
- Glycerol	0.500 g
- 70% sorbitol	0.500 g
- Sodium saccharinate	0.010 g
- Methyl parahydroxybenzoate	0.040 g
- Flavouring	qs
- Purified water	q.s. 5 ml

B- TOPICAL ADMINISTRATION

(a) Unguent

- Compound (**I.2**)	0.300 g
- White petroleum jelly codex	q.s. 100 g

(d) Lotion

- Compound (**I.4**)	0.100 g
- Polyethylene glycol (PEG 400)	69.900 g
- 95% ethanol	30.000 g

(e) Hydrophobic unguent

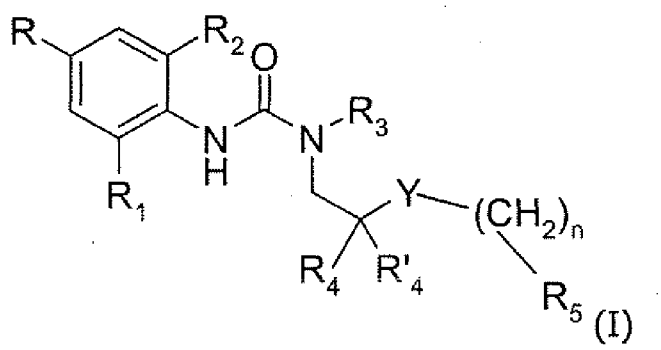
- Compound (**I.1**)	0.300 g
- Isopropyl myristate	36.400 g
- Silicone oil ("Rhodorsil 47 V 300")	36.400 g
- Beeswax	13.600 g
- Silicone oil ("Abil 300,000 cSt")	q.s. 100 g

(f) Non-ionic oil-in-water cream

- Compound (**I.2**)	1.000 g
- Cetyl alcohol	4.000 g
- Glycerol monostearate	2.500 g
- Stearate of PEG 50	2.500 g
- Shea butter	9.200 g
- Propylene glycol	2.000 g
- Methyl parahydroxybenzoate	0.075 g
- Propyl parahydroxybenzoate	0.075 g
- Sterile demineralized water	q.s. 100 g

Patent claims

1. Compounds of formula (I):



(I)

in which

- Y represents O or $S(O)_p$,

- p is equal to 0 or 2,

- n is equal to 0, 1 or 2

- R represents a hydrogen atom, a (C_1-C_6)alkyl group, a $-CH_2-NR_6R_7$ group, a $-C(O)-NR_6R_7$ group or a $-C(S)-NR_6R_7$ group, where R_6 represents a hydrogen atom or a (C_1-C_4)alkyl group and R_7 represents a hydrogen atom, a phenyl or a cycloalkyl group,

- R_1 represents a hydrogen atom, a (C_1-C_6)alkyl group or an atom of chlorine, bromine or fluorine,

- R_2 represents a (C_1-C_6)alkyl group,

- R_3 represents a hydrogen atom or a (C_1-C_6)alkyl group,

- R_4 and R'_4 are identical and represent a (C_1-C_6)alkyl group or alternatively R_4 and R'_4 are joined together and form, with the carbon atom to which they are

attached, a cycloalkyl group, an indanyl group, or a saturated heterocyclic group selected from the groups piperidine, tetrahydropyran, pyrrolidine, tetrahydrothiophene, tetrahydrofuran and azetidine, moreover the groups piperidine, pyrrolidine and azetidine can optionally be substituted on the nitrogen atom with an R_8, $-C(O)R_8$ or $-SO_2R_8$ group, where R_8 represents a (C_1-C_4)alkyl group,

- R_5 represents an unsubstituted phenyl group or a phenyl group substituted with one to three substituents, which may be identical or different, selected from the atoms of chlorine, bromine or fluorine, the groups (C_1-C_6)alkyl, cycloalkyl, trifluoromethyl, hydroxy, phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, (C_1-C_6)alkoxy, phenoxy, (C_1-C_6)alkylthio, trifluoromethoxy, or $-NR_9R_{10}$, where R_9 and R_{10}, which may be identical or different, represent, each independently, a hydrogen atom or a (C_1-C_4)alkyl group,

as well as their pharmaceutically acceptable salts, solvates or hydrates.

2. Compounds according to Claim 1, characterized in that:

- Y represents O, $S(O)_p$,

- p is equal to 0 or 2,

- n is equal to 0, 1 or 2,

- R represents a hydrogen atom,

- R_1 represents a methyl, ethyl, isopropyl or *tert*-butyl group,

- R_2 represents a methyl, ethyl, isopropyl or *tert*-butyl group,

- R_3 represents a hydrogen atom,

- R_4 and R'_4 are identical and represent an ethyl group or alternatively R_4 and R'_4 are joined together and form, with the carbon atom to which they are attached, either a cyclopentyl, cyclohexyl, cycloheptyl, or indanyl group, or a tetrahydropyran group, piperidine group, or piperidine group substituted on the nitrogen atom with an R_8, $-C(O)R_8$ or $-SO_2R_8$ group, where R_8 represents a (C_1-C_4)alkyl group,

- R_5 represents an o-, m- or p-biphenyl, o-, m- or p-iodophenyl, o-, m- or p-(2-pyridyl)phenyl, o-, m- or p-(3-pyridyl)phenyl or an o-, m- or p-(4-pyridyl)phenyl group, an unsubstituted phenyl group, a phenyl group substituted with one to three substituents, identical or different, selected from methyl, ethyl, trifluoromethyl, fluorine, chlorine, hydroxy.

3. Compounds according to Claim 1 or 2, characterized in that n is equal to 0 or 1.

4. Compounds according to one of Claims 1 to 3, characterized in that R represents a hydrogen atom.

5. Compounds according to one of Claims 1 to 4, characterized in that R_1 represents an isopropyl group.

6. Compounds according to one of Claims 1 to 5, characterized in that R_2 represents an isopropyl group.

7. Compounds according to one of Claims 1 to 6, characterized in that R_3 represents a hydrogen atom.

8. Compounds according to one of Claims 1 to 7, characterized in that R_4 and R'_4 are joined together and form, with the nitrogen atom to which they are attached, a cyclopentyl, cyclohexyl or indanyl group.

9. Compounds according to one of Claims 1 to 8, characterized in that R_5 represents an unsubstituted phenyl group, or a phenyl group substituted with a methyl group or with a phenyl group.

10. Compound according to Claim 1, selected from the following compounds, their pharmaceutically acceptable salts, solvates and hydrates:
-1-(1-Benzenesulphonyl-cyclopentylmethyl)-3-(2,6-diisopropyl-phenyl)-urea,
-1-(2,6-Diisopropyl-phenyl)-3-[1-(toluene-4-sulphonyl)-cyclopentylmethyl]-urea,
-1-(2-Benzenesulphonyl-indan-2-ylmethyl)-3-(2,6-diisopropyl-phenyl)-urea,
-1-(1-Benzylsulphanyl-cyclohexylmethyl)-3-(2,6-diisopropyl-phenyl)-urea,
-1-(1-Benzyloxy-cyclohexylmethyl)-3-(2,6-diisopropyl-phenyl)-urea,
-1-(2,6-Diisopropyl-phenyl)-3-(1-phenoxy-cyclohexylmethyl)-urea,
-1-(2,6-Diisopropyl-phenyl)-3-(1-phenylsulphanyl-cyclohexylmethyl)-urea,
-1-(2,6-Diisopropyl-phenyl)-3-(1-p-tolylsulphanyl-cyclohexylmethyl)-urea,
-1-[1-(Biphenyl-2-ylsulphanyl)-cyclohexylmethyl]-3-(2,6-diisopropyl-phenyl)-urea,
-1-[1-(Biphenyl-2-ylsulphanyl)-cyclopentylmethyl]-3-(2,6-diisopropyl-phenyl)-urea,
-1-[1-(Biphenyl-2-yloxy)-cyclohexylmethyl]-3-(2,6-diisopropyl-phenyl)-urea.

11. Compounds according to one of the preceding claims, as medicinal products.

12. Pharmaceutical composition comprising, in a physiologically acceptable carrier, at least one compound according to one of Claims 1 to 10.

13. Composition according to Claim 12, characterized in that the concentration of compound(s) according to any one of Claims 1 to 10 is between 0.001 and 10 wt.% relative to the total weight of the composition.

14. Composition according to Claim 13, characterized in that the concentration of compound(s) according to any one of Claims 1 to 10 is between 0.01 and 2 wt.% relative to the total weight of the composition.

15. Cosmetic composition, characterized in that it comprises, in a physiologically acceptable carrier, at least one compound according to any one of Claims 1 to 10.

16. Composition according to Claim 15, characterized in that the concentration of compound(s) according to any one of Claims 1 to 10 is between 0.001 and 3 wt.% relative to the total weight of the composition.

17. Composition according to one of Claims 12 to 16, characterized in that it is in a form suitable for topical application.

18. Composition according to Claim 17, characterized in that it is in the form of a cream, a milk, a lotion, a gel, an unguent, an ointment, suspensions of microspheres or nanospheres or lipid or polymeric vesicles, impregnated tampons, solutions, sprays, mousses, sticks, soaps, shampoos or washing bases.

19. Cosmetic use of a composition as defined in either of Claims 15 or 16 for body or hair hygiene.

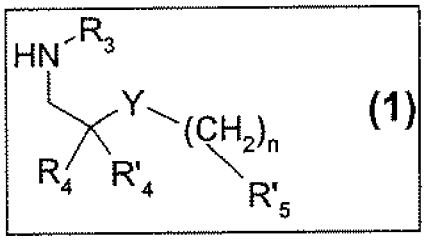
20. Use of a compound according to any one of Claims 1 to 9 in the manufacture of a medicinal product for preventing and/or treating disorders of the sebaceous gland such as hyperseborrhoea, acne, seborrhoeic dermatitis, atopic dermatitis, rosacea, ocular rosacea,

blepharitis, meibomitis, chalazion, dry eye, conjunctivitis or keratoconjunctivitis, hypercholesterolaemia, arteriosclerosis and Alzheimer's disease.

21. Use of a compound according to any one of Claims 1 to 10 for the manufacture of a medicinal product for the treatment of acne.

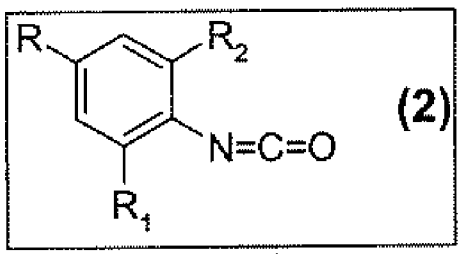
22. Method of preparation of the compounds of formula (I) according to one of Claims 1 to 10, characterized in that it comprises the following stages:

a primary or secondary amine of formula (**1**):

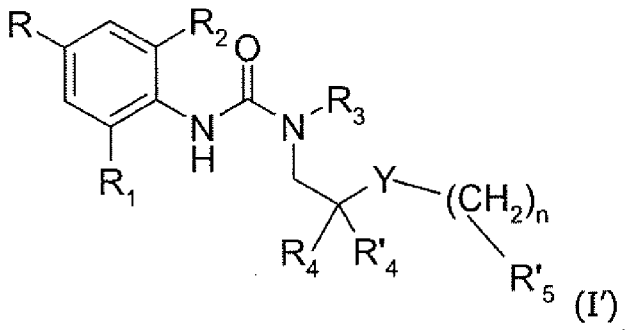


in which R_3, R_4, R'_4, n and Y are as defined in Claim 1, and R'_5 represents the group R_5 as defined in Claim 1 or a precursor of the group R_5,

is reacted with a compound of formula (**2**):



in which R, R_1 and R_2 are as defined in Claim 1, to obtain the compound of formula (I'):



(I')

in which R, R_1, R_2, R_3, R_4, R'_4, Y and n are as defined in Claim 1, and R'_5 represents the group R_5 as defined in Claim 1 or a precursor of the group R_5,

then, when R'_5 is different from R_5, the group R'_5 is transformed to obtain the desired group R_5.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/061779

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C317/30 C07C323/30 C07C275/28 A61K31/17 A61K8/46
A61K8/40 A61Q19/00 A61P17/08 A61P17/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 106 873 A (P.M. O'BRIEN, ET AL.) 21 April 1992 (1992-04-21) cited in the application column 1, line 58 - column 5, line 56; examples 2,4,5 ----- -/--	1-22

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 December 2008	23/12/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	English, Russell

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/061779

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	P.M. O'BRIEN, ET AL.: "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 8. Incorporation of amide or amine functionalities into a series of disubstituted ureas and carbamates. Effects on ACAT inhibition in vitro and efficacy in vivo" JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 12, 10 June 1994 (1994-06-10), pages 1810-1822, XP002082610 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US ISSN: 0022-2623 compounds 24a, 24b and 24c	1-22
A	B.K. TRIVEDI, ET AL.: "Inhibitors of acyl-CoA:cholesterol acyltransferase. 4. A novel series of urea ACAT inhibitors as potential hypocholesterolaemic agents" JOURNAL OF MEDICINAL CHEMISTRY, vol. 36, no. 22, 29 October 1993 (1993-10-29), pages 3300-3307, XP000617639 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US ISSN: 0022-2623 tables I-V	1-22
A	R. BELLEMIN, ET AL.: "New indole derivatives as ACAT inhibitors: synthesis and structure-activity relationships" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 31, no. 2, 1996, pages 123-132, XP004040099 EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR ISSN: 0223-5234 table IV	1-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/061779

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5106873 A	21-04-1992	NONE	